

What is claimed is:

1. A pharmaceutical composition for inducing tissue formation in a mammal, comprising:

5 a) a morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell in the mammal;

b) a morphogenic protein stimulatory factor capable of stimulating the ability of the morphogenic protein to induce tissue formation from the progenitor cell; and

10 c) a pharmaceutically acceptable carrier.

2. A pharmaceutical composition for inducing tissue formation in a mammal, comprising:

15 a) a morphogenic protein comprising a pair of subunits disulfide bonded to produce a dimeric species capable of inducing tissue formation when accessible to a progenitor cell in the mammal, wherein at least one of the subunits comprises a polypeptide belonging to the BMP protein family;

20 b) a morphogenic protein stimulatory factor capable of stimulating the ability of the morphogenic protein to induce tissue formation from the progenitor cell; and

c) a pharmaceutically acceptable carrier.

3. A pharmaceutical composition for inducing tissue formation in a mammal, comprising:

25 a) an morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell in the mammal, wherein the morphogenic protein is an osteogenic protein;

30 b) a morphogenic protein stimulatory factor capable of stimulating the ability of the osteogenic protein to induce tissue formation from the progenitor cell; and

c) a pharmaceutically acceptable carrier.

4. The composition according to any one of claims 1-3, wherein the morphogenic protein is an osteogenic protein that is capable of inducing the progenitor cell to form endochondral or intramembranous bone.

5 5. The composition according to claim 4, wherein the osteogenic protein is capable of inducing the progenitor cell to form cartilage.

10 6. The composition according to any one of claims 1-3, wherein the morphogenic protein is capable of inducing the progenitor cell to form tissue tendon/ligament-like or neural-like tissue.

15 7. The composition according to any one of claims 1-3, wherein the morphogenic protein comprises a polypeptide selected from the group consisting of: BMP-2, BMP-4, BMP-5, BMP-6, BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, and BMP-13, COP-5, COP-7.

20 8. The composition according to any one of claims 1-3, wherein the morphogenic protein comprises a polypeptide selected from the group consisting of OP-1, BMP-2, BMP-4 and BMP-6.

9. The composition according to any one of claims 1-3, wherein the morphogenic protein comprises OP-1.

25 10. The composition according to claim 2, wherein the dimer is a homo- or a heterodimer comprising at least one BMP-2 or OP-1 (BMP-7) subunit.

11. The device according to any one of claims 1-3, wherein the morphogenic protein is produced by the expression of a recombinant DNA molecule in a host cell.

12. The composition according to any one of claims 1-3, wherein the morphogenic protein stimulatory factor comprises at least one compound selected from the group consisting of: insulin-like growth factor I (IGF-I), estradiol, fibroblast growth factor (FGF), growth hormone (GH), growth and differentiation factor (GDF), hydrocortisone (HC), insulin, progesterone, parathyroid hormone (PTH), vitamin D, retinoic acid and IL-6.

13. The composition according to any one of claims 1-3, wherein the morphogenic protein stimulatory factor comprises an agent that increases IGF-I bioactivity in the mammal.

14. The composition according to any one of claims 1-3, wherein the morphogenic protein stimulatory factor is present in an amount capable of synergistically stimulating the ability of the morphogenic protein to induce tissue formation in the mammal.

15. The composition according to any one of claims 1-3, wherein the morphogenic protein is present at a concentration of at least about 1 ng/ml, and the morphogenic protein stimulatory factor is present at a concentration of at least about 0.01 ng/ml.

16. The composition according to any one of claims 1-3, wherein the morphogenic protein comprises OP-1 at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor comprises IGF-I at a concentration from about 0.1 ng/ml to about 50 ng/ml.

17. The composition according to claim 16, comprising 200 ng/ml of OP-1 and 25 ng/ml of IGF-I.

18. The composition according to any one of claims 1-3, wherein the morphogenic protein comprises OP-1 at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor comprises estradiol at a concentration of from about 0.05 nM to about 1000 nM.

19. The composition according to claim 18, comprising about 200 ng/ml of OP-1 and about 5 nM estradiol.

20. The composition according to any one of claims 1-3, wherein the morphogenic protein comprises OP-1 at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor comprises growth hormone at a concentration of from about 5 ng/ml to about 1000 ng/ml.

21. The composition according to claim 20, comprising about 200 ng/ml of OP-1 and about 500 - 1000 ng/ml growth hormone.

22. The composition according to any one of claims 1-3, wherein the morphogenic protein comprises OP-1 at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor comprises hydrocortisone at a concentration of from about 0.05 nM to about 5.0 nM.

23. The composition according to claim 22, comprising about 200 ng/ml OP-1 and about 0.5 - 5.0 nM hydrocortisone.

24. The composition according to any one of claims 1-3, wherein the morphogenic protein comprises OP-1 at a

concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor comprises insulin at a concentration of from about 0.01 nM to about 1000 nM.

5 25. The composition according to claim 24, comprising about 200 ng/ml OP-1 and about 0.05 nM insulin.

10 26. The composition according to any one of claims 1-3, wherein the morphogenic protein comprises OP-1 at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor comprises parathyroid hormone at a concentration of from about 10 nM to about 1000 nM.

27. The composition according to claim 26, comprising about 200 ng/ml OP-1 and about 25-200 nM parathyroid hormone.

15 28. The composition according to any one of claims 1-3, wherein the morphogenic protein comprises OP-1 at a concentration of from about 1 ng/ml to about 500 ng/ml and the morphogenic protein stimulatory factor comprises progesterone at a concentration of from about 0.05 nM to about 1000 nM.

20 29. The composition according to claim 28, comprising about 200 ng/ml OP-1 and about 0.05 - 5 nM progesterone.

30. A morphogenic device for implantation in a mammal, the device comprising:

- 25 a) an implantable biocompatible carrier,
- b) a morphogenic protein disposed in the carrier, the morphogenic protein capable of inducing tissue formation when accessible to a progenitor cell, and
- c) a morphogenic protein stimulatory factor disposed in the carrier, the stimulatory factor capable of

stimulating the ability of the morphogenic protein to induce tissue formation from the progenitor cell.

31. A morphogenic device for implantation in a mammal, the device comprising:

5 a) an implantable biocompatible carrier,
 b) a morphogenic protein disposed in the carrier, the morphogenic protein comprising a pair of subunits disulfide bonded to produce a dimeric species capable of inducing tissue formation when accessible to a progenitor cell,
10 wherein at least one of the subunits comprises a polypeptide belonging to the BMP protein family, and

 c) a morphogenic protein stimulatory factor disposed in the carrier, the stimulatory factor capable of stimulating the ability of the morphogenic protein to induce
15 tissue formation from the progenitor cell.

32. A morphogenic device for implantation in a mammal, the device comprising:

 a) an implantable biocompatible carrier,
 b) a morphogenic protein disposed in the carrier,
20 wherein the morphogenic protein is an osteogenic protein; and

 c) a morphogenic protein stimulatory factor disposed in the carrier, the stimulatory factor capable of stimulating the ability of the osteogenic protein to induce
25 tissue formation from the progenitor cell.

33. The device according to any one of claims 30-32, wherein the carrier further comprises a biocompatible matrix.

34. The device according to claim 33, wherein the matrix
30 comprises demineralized, protein-extracted, particulate, allogenic bone.

35. The device according to claim 33, wherein the matrix comprises mineral-free, delipidated Type I insoluble bone collagen particles, substantially depleted in noncollagenous protein.

5 36. The device according to any one of claims 30-32, wherein the morphogenic protein is an osteogenic protein that is capable of inducing the progenitor cell to form endochondral or intramembranous bone.

10 37. The device according to any one of claims 30-32, wherein the morphogenic protein is an osteogenic protein that is capable of inducing the progenitor cell to form cartilage.

15 38. The device according to any one of claims 30-32, wherein the morphogenic protein is capable of inducing the progenitor cell to form tendon/ligament-like or neural-like tissue.

20 39. The device according to any one of claims 30-32, wherein the morphogenic protein comprises a polypeptide selected from the group consisting of: BMP-2, BMP-4, BMP-5, BMP-6, BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, and BMP-13, COP-5 and COP-7.

25 40. The device according to any one of claims 30-32, wherein the morphogenic protein comprises a polypeptide selected from the group consisting of OP-1, BMP-2, BMP-4 and BMP-6.

41. The device according to any one of claims 30-32, wherein the morphogenic protein comprises OP-1.

42. The device according to claim 31, wherein the dimer is a homo- or heterodimer comprising at least one BMP-2 or OP-1 subunit.

43. The device according to any one of claims 30-32,
5 wherein the morphogenic protein is produced by the expression of a recombinant DNA molecule in a host cell.

44. The device according to claim 43, wherein the morphogenic protein comprises at least one subunit comprising an amino acid sequence sufficiently duplicative
10 of the amino sequence of COP-5 or COP-7 such that the species is capable of inducing tissue formation in a mammal when disposed in the carrier and implanted in the mammal.

45. The device according to any one of claims 30-32,
15 wherein the morphogenic protein stimulatory factor comprises at least one compound selected from the group consisting of: insulin-like growth factor I (IGF-I), estradiol, fibroblast growth factor (FGF), growth hormone (GH), growth and differentiation factor (GDF), hydrocortisone (HC), insulin, progesterone, parathyroid hormone (PTH), vitamin D, retinoic
20 acid and IL-6.

46. The device according to any one of claims 30-32,
wherein the morphogenic protein is present at a concentration of at least about 1 ng/ml, and the morphogenic protein stimulatory factor is present at a concentration of
25 at least about 0.01 ng/ml.

47. The device according to any one of claims 30-32,
comprising a composition according to any one of claims 15-28.

48. A method for improving the tissue inductive activity of a morphogenic protein in a mammal by coadministering an effective amount of a morphogenic protein stimulatory factor.

5 49. The method according to claim 48, wherein the morphogenic stimulatory factor has additive effects on tissue induction by the morphogenic protein.

10 50. The method according to claim 48, wherein the morphogenic stimulatory factor has synergistic effects on tissue induction by the morphogenic protein.

51. The method according to claim 48, wherein the morphogenic protein is an osteogenic protein that is capable of inducing the progenitor cell to form endochondral or intramembranous bone.

15 52. The method according to claim 48, wherein the morphogenic protein is an osteogenic protein that is capable of inducing the progenitor cell to form cartilage.

20 53. The method according to claim 48, wherein the morphogenic protein is an osteogenic protein that is capable of inducing the progenitor cell to form tendon/ligament-like or neural tissue.

25 54. The method according to claim 48, wherein the morphogenic protein comprises a polypeptide selected from the group consisting of: BMP-2, BMP-4, BMP-5, BMP-6, OP-1 (BMP-7), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, and BMP-13, COP-5 and COP-7.

55. The method according to claim 48, wherein the morphogenic protein comprises a disulfide bonded dimeric species comprising a polypeptide selected from the group consisting of OP-1, BMP-2, BMP-4 and BMP-6.

5 56. The method according to claim 48, wherein the morphogenic protein comprises OP-1.

57. The method according to claim 48, wherein the morphogenic protein is produced by the expression of a recombinant DNA molecule in a host cell.

10 58. The method according to claim 48, wherein the morphogenic protein stimulatory factor comprises at least one compound selected from the group consisting of:
15 insulin-like growth factor I (IGF-I), estradiol, fibroblast growth factor (FGF), growth hormone (GH), growth and differentiation factor (GDF), hydrocortisone (HC), insulin, progesterone, parathyroid hormone (PTH), vitamin D, retinoic acid and IL-6.

20 59. The method according to claim 48, wherein the morphogenic protein stimulatory factor is present in an amount capable of synergistically stimulating the ability of the morphogenic protein to induce tissue formation in the mammal.

25 60. An implantable prosthetic device for repairing orthopedic defects, injuries or anomalies in a mammal, comprising:

- a) a prosthetic implant having a surface region implantable adjacent to a target tissue in the mammal; and
- b) a composition comprising an osteogenic protein and a morphogenic protein stimulatory factor disposed on the

surface region in an amount sufficient to promote enhanced tissue growth into the surface.

61. The prosthetic device according to claim 60, wherein the osteogenic protein is capable of inducing the progenitor cell to form a tissue selected from the group consisting of endochondral bone, intramembranous bone, cartilage, tendon/ligament-like tissue and neural tissue.

62. The prosthetic device according to claim 60, wherein the osteogenic protein comprises a polypeptide selected from the group consisting of: BMP-2, BMP-4, BMP-5, BMP-6, OP-1 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, and BMP-13, COP-5 and COP-7.

63. The prosthetic device according to claim 60, wherein the osteogenic protein comprises a disulfide bonded dimeric species comprising a polypeptide selected from the group consisting of OP-1, BMP-2, BMP-4 and BMP-6.

64. The prosthetic device according to claim 60, wherein the osteogenic protein comprises OP-1.

65. The prosthetic device according to claim 60, wherein the osteogenic protein is produced by the expression of a recombinant DNA molecule in a host cell.

66. The prosthetic device according to claim 60, wherein the morphogenic protein stimulatory factor comprises at least one compound selected from the group consisting of: insulin-like growth factor I (IGF-I), estradiol, fibroblast growth factor (FGF), growth hormone (GH), growth and differentiation factor (GDF), hydrocortisone (HC), insulin, progesterone, parathyroid hormone (PTH), vitamin D, retinoic acid and IL-6.

67. The prosthetic device according to claim 60, wherein the morphogenic protein stimulatory factor comprises an agent that increases IGF-I bioactivity in the mammal.

5 68. The device according to claim 60, wherein the morphogenic protein stimulatory factor is present in an amount capable of synergistically stimulating the ability of the morphogenic protein to induce tissue formation in the mammal.

10 69. A method for inducing local tissue formation from a progenitor cell in a mammal comprising the step of implanting in the mammal a morphogenic device according to any one of claims 30-47 at a locus accessible to at least one progenitor cell of the mammal.

15 70. The method according to claim 69, wherein the locus is a jaw bone for use in periodontal or dental reconstructive procedures.

71. The method according to claim 69, wherein the locus is a bone defect selected from the group consisting of a fracture, a non-union fracture, a fusion and a bony void.

20 72. The method according to claim 69, wherein the locus is a joint for use in cartilage and soft tissue repair.

73. The method according to claim 69, wherein the locus is nervous system-associated tissue for use in neural regeneration and repair.

25 74. A method of accelerating allograft repair and incorporation in a mammal, comprising the step of implanting at a locus in need of replacement bone a matrix-comprising device according any one of claims 30-32.

75. The method according to claim 74, wherein the matrix of the device comprises allogenic bone.

76. A method of promoting in vivo integration into a target tissue of a mammal an implantable prosthetic device, the method comprising the steps of:

a) providing on a surface of the prosthetic device a composition according to any one of claims 60-68, and

b) implanting the device in a mammal at a locus where the target tissue and the surface of the prosthetic device are maintained at least partially in contact for a time sufficient to permit enhanced tissue growth between the target tissue and the device.

77. A method of treating a tissue degenerative condition in a mammal comprising the step of administering a pharmaceutical composition according to any one of claims 1-29.

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